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Spinal Cord Stimulation is not Cost-effective for Non-surgical Management of Critical Limb Ischaemia

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Objective. *To quantify the costs of treatment in critical limb ischaemia (CLI) and to compare costs and effectiveness of two treatment strategies: spinal cord stimulation (SCS) and best medical treatment.*
Methods. *One hundred and twenty patients with CLI not suitable for vascular reconstruction were randomised to either SCS in addition to best medical treatment or best medical treatment alone. Primary outcomes were mortality, amputation and cost. Cost analysis was based on resources used by patients for 2 years after randomisation. Both medical and non-medical costs were included.*
Results. *Patient and limb survival were similar in the two treatment groups. Costs of in-hospital-stay and institutional rehabilitation constituted the predominant part (±70%) of the total costs of medical care in CLI. Cost of SCS-implantation and complications (€7950 per patient) exceeded by far cost due to amputation procedures (€410 per patient). The total costs of treatment were €36,600 per patient over 2 years for the SCS-group* vs. *€28,700 for best medical treatment alone (28% higher for SCS-group,* $p=0.009$*).*
Conclusions. *Total costs of treatment in CLI are high. Major components are hospital and rehabilitation costs. In contrast to recent reviews, there were no long-term benefits of SCS-treatment. Therefore, cost-effectiveness is reduced to cost-minimisation and SCS-treatment is considerably more expensive than best medical treatment.*

Keywords: Cost analysis; Cost-effectiveness; Critical limb ischaemia; Spinal cord stimulation; Electrical stimulation; Meta-analysis; Peripheral vascular disease; Prognosis; Risk factors; Survival; Trials.

Background

Critical limb ischaemia (CLI) threatens the survival of an extremity and often causes lifelong disablement from a painful leg. Lower-extremity amputation bears a high risk of disability, prolonged institutionalisation or death.[1–4] Compared with amputation, revascularisation is associated with better perioperative morbidity and mortality. Limb preservation should be the goal, yet many patients with critical leg ischaemia are poor candidates for the preferred therapeutic options of percutaneous transluminal angioplasty or surgical revascularisation.

Many authors have recommended the use of spinal cord stimulation (SCS) in patients with limb-threatening ischaemia in whom vascular reconstruction is not an option.[5–19] SCS involves implantation of a pacemaker with epidural lead activating the dorsal columns of the spinal cord. Dorsal column stimulation at Th10-L1 level induces paraesthesia in the lower extremities, thereby alleviating ischaemic pain. Pain relief has been reported as excellent in CLI and limb survival far better than expected (68–80% after 1 year).[6,8,12,20,21] In a multicentre randomised trial,[22] we found that SCS-treatment was no more effective than best medical treatment alone in preventing amputations. Recently, however, several reviews concluded that SCS is beneficial (in selected patients).[18,19,23] Since these reviews contain major weaknesses and the available information on costs in CLI involved is very limited,[24–26] we present a reconsideration of the evidence together with a detailed analysis of costs.

If costs were considered in CLI, often these were ‘roughly’ calculated using charges/fees and with little

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information about the differentiation of the costs. This may result in bias.

We aimed to study the total direct and indirect medical costs of critical limb ischaemia within the framework of a randomised trial. We present estimates of the full cost price, based on real resource use, in substantial patient groups.

Methods

Study design

The trial design has been published.[22,27] In brief, patients with CLI as characterized by persisting rest pain or ischaemic skin lesions[1] were eligible, if vascular reconstruction was not possible. From 17 hospitals in The Netherlands, 120 patients were enrolled from 1991 until 1996. The ethical committees at each participating centre approved the study protocol, and patients gave written informed consent. The treatment strategies SCS in addition to best medical treatment ('SCS-treatment') and best medical treatment alone ('standard treatment') were allocated at random to eligible patients using balanced block randomisation.

Treatment

Standard treatment included analgesics, antithrombotic and haemorrheologic drugs, local wound care and antibiotics, if indicated. There was a list of recommended medication, but no fixed treatment regimen. Those patients allocated to SCS treatment additionally received an implantable spinal cord stimulation system. A quadripolar lead (Medtronic) was placed in the epidural space and connected to an Itrell II pulse generator (Medtronic). Both treatment regimens initially aimed at adequate pain suppression. During follow-up, the treatment effect was optimised by altering medication, stimulation settings or both. Patients receiving SCS-treatment were checked regularly by a neurosurgeon or anaesthesiologist.

All patients were assessed before randomisation, at 1, 3, 6, 12, 18 months after randomisation, and at the end of the study. After each follow-up visit, patients completed a questionnaire on consumption of health resources. Between follow-up visits patients came to the hospital as often as necessary. The primary outcome measure was limb survival, defined as absence of 'major' amputation (on level of foot or higher).[28]

Background of the cost analysis

The viewpoint of the cost analysis was societal, thus all costs and consequences were taken into account. Cost analysis was based on recorded resource use by patients for 2 years after randomisation or until death, if this occurred within 2 years. The costs were calculated per patient as the product of volumes and market prices. Volumes of the cost items were collected for all patients. Market prices were estimated in smaller samples. All costs were converted to 1993 Euros (DFL 100 = €4538), according to the calculation factor of the The Nederlandsche Bank (www.dnb.nl). Costs were not discounted given the short time perspective (2 years per patient). In the successive time periods (0–1, 1–3, 3–6 months after randomisation, etc.) volumes of resource use per patient were calculated from the observed volumes divided by the number of patients at risk. This method was an adaptation of the product-limit method as used in survival analysis.[29]

Use of resources

Costs were classified into direct medical costs (inside and outside the hospital), direct non-medical costs and indirect costs.[30] The components of the medical costs in CLI are summarized in Table 2. Direct non-medical costs consisted of travel expenses and out-of-pocket expenses on home adaptations (e.g. removal of thresholds for wheelchairs, bathroom adaptations). Indirect non-medical costs involved non-professional help to patients externally to the health sector (e.g. transportation by relatives and friends or domestic help). We did not include costs caused by loss of production due to absence from work, since the majority of patients were retired from work.

Hospital admissions were classified as directly related to CLI (wound care, amputations, complications), related to CLI (other vascular events, including cardio- and cerebrovascular events) or not related to CLI. In The Netherlands, nursing homes have adequate facilities for rehabilitation; therefore, temporary stay in nursing homes is common for elderly amputees. As for homes for the elderly, only new admissions (after randomisation) were taken into account.

Volume information on outpatient visits, direct medical cost items outside the hospital and non-medical care was primarily collected from patient questionnaires. Data on operative procedures, in-hospital stay and rehabilitation, and medication usage were available from the case-record-forms filled in by the surgeons. Furthermore, information was checked in hospital administrations and hospital information systems.

Costing resources

For evaluation of the costs, we first identified the fundamental cost items. A detailed cost analysis was performed to estimate market prices for the important determinants, i.e. those with large volumes or high prices. These were primarily direct medical costs, such as in-hospital-stay, operative procedures, and admission to nursing home or rehabilitation clinic. For minor cost items, as travel expenses and out-of-pocket payments, charges or expert estimates were used as approximations of the market prices.

Hospital admission prices were assessed in detail, using cost registrations to quantify attendance by health professionals, supplies, equipment, and capital costs (fixed annual costs of running the unit). We estimated prices of lower limb amputations by recording the presence and time of various health professionals during amputation procedures. Registrations were performed in one university hospital and two general hospitals. Prices of supplies, equipment, and capital costs were obtained from a detailed department based cost registration. These data were available from the hospital information system. The price of implantation of the SCS device was estimated using presence of personnel and time registrations during 20 consecutive implantation procedures; yet the main costs of SCS-implantation arose from the price of the Itrell II pulse generator and Quad lead (€7200). The prices of outpatient visits were based on department based cost registrations. Prices of admission to a nursing home or rehabilitation clinic were available from other Dutch national investigations.[31,32] Prices for rehabilitation were adjusted according to expert opinion on the amount of medical care consumed by vascular amputees in relation to the average patient in a rehabilitation clinic.

Statistical analysis

All data were recorded on standardized forms and entered in a concurrent database. Analysis of both clinical outcome and cost was by 'intention to treat' and included all randomised patients. Patient and limb survival were estimated and compared with Kaplan–Meier analysis and log-rank tests. In the analysis of limb survival, patients were censored at death. Cost differences between groups were analysed by Mann–Whitney test. For all hypothesis tests, p-values are stated, with $p<0.05$ interpreted as statistically significant.

Results

Sixty patients were randomly assigned to receive SCS-treatment and 60 to receive standard treatment. Mean duration of hospitalisation for SCS-implantation was 4.9 ($\pm$2.3) days. In two patients, adequate implantation proved to be impossible, and one patient refused implantation. The two treatment groups were comparable in terms of demographic and clinical characteristics. Mean age was 72.6 (range 38–89) years, 58% were males, 38% had diabetes, and 68% were (former) smokers (Table 1). Median follow-up was 2 years (range 8–59 months).

There was no significant difference in patient and limb survival between the two treatment groups (Fig. 1). Cumulative patient survival at 2 years was 64% in the SCS-group *vs.* 63% in the standard group (HR=1.09, p=0.96). Limb survival at 2 years was 52 and 46%, respectively (HR=0.82, p=0.47). Analysis of amputation levels revealed no significant differences. In the SCS-group, 18 complications (lead displacements or inadequate stimulation) were treated by operative repositioning procedures.

In Table 2, the unit costs for applicable cost items are summarized, with separate information for university

Table 1. Baseline characteristics of the SCS and standard treatment groups

Characteristics	SCS (n=60)	Standard (n=60)
Male/female	33/27 (55/45%)	37/23 (62/38%)
Age [year]	73.1±9.8	72.1±10.6
Diabetes	22 (37%)	23 (38%)
'Other leg'		
Symptomatic	19 (32%)	29 (48%)
Amputated	9 (15%)	7 (12%)
Smoking		
Quitted >1 year	22 (37%)	16 (27%)
Still smoking	18 (30%)	26 (44%)
CVA or TIA	13 (22%)	16 (27%)
Myocardial infarction	23 (38%)	22 (37%)
Angina pectoris	12 (20%)	15 (25%)
Rest pain only	22 (37%)	19 (32%)
Ischaemic skin lesions	38 (63%)	41 (68%)
Gangrene	24 (40%)	23 (38%)
Vasc. reconstructions		
Nil	11 (18%)	15 (25%)
1 or 2	25 (42%)	29 (48%)
>3	19 (32%)	20 (33%)
Sympathectomy	21 (35%)	19 (32%)
Ankle systolic pressure [mmHg]	35.2±25	41.6±22
Ankle-to-brachial pressure index	0.23±0.16	0.28±0.13

Data are number (%) or mean±SD.

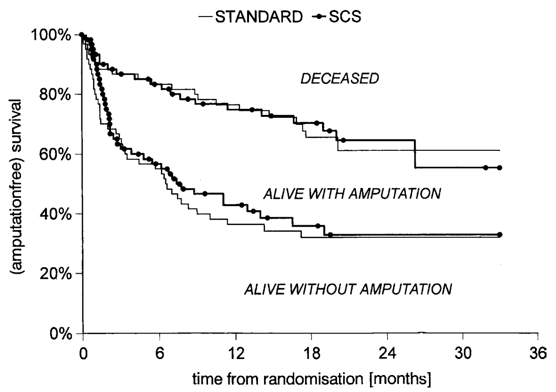

Fig. 1. Mortality and amputation in CLI. The upper curves indicate patient survival for both treatment groups ('SCS' and 'standard' treatment); the lower curves indicate amputation free survival. The area between the upper and lower curves represents the proportion of patients alive with major amputation. Patients at risk: at 12 months 47/44, at 24 months 21/19.

and general hospitals. Table 3 shows how long the patients spent in hospital, rehabilitation centre and nursing home in both treatment groups. Most in-hospital days (over 80%) were directly related to CLI. Only four intensive care unit days were noted (in the standard group). Although in the SCS-group patients spent less days in rehabilitation clinics, there were more admissions to nursing homes. Consequently, the costs of rehabilitation (in clinics and nursing homes together) were similar (€6760 *vs.* 7480 at 2 years). Costs of in-hospital-stay and institutional rehabilitation constituted the predominant part of the total costs of medical care in CLI. Table 4 shows mean cumulative costs per patient according to cost type for both treatments.

Obviously, cost for operative procedures was much higher in the SCS-group because of implantation of the SCS-device (€7770). In the first month after randomisation more in-hospital days in the SCS-group occurred, due to hospitalisation for the implantation procedure. Over a 2-year period, cost of SCS-implantation and complications (€7950 per patient) far exceeded the cost due to amputation procedures (€410 per patient). Outpatient cost was higher for SCS-treatment, because of checkups by the neurosurgeon or anaesthesiologist. In the SCS-group more patients moved to homes for the elderly, while in the standard group more patients received professional care in their own home. Again, combined societal costs for homes for the elderly and domestic professional care were comparable in SCS- and standard group (€6120 *vs.* €5040). For both medication and medical supplies, costs were lower in the SCS group by about 30%. Direct and indirect non-medical costs had little impact, but were somewhat higher for SCS-treatment. Fig. 2 shows the total cost and its components over 2 years. After 2 years of treatment, costs of SCS-treatment per patient were €7900 (28%) higher as compared to standard treatment (€36,600 *vs.* 28,700, $p=0.009$).

Since, mortality was high (23% of the patients died within 1 year, 36% within 2 years), a considerable proportion of patients did not contribute to the cost increase during the entire time period of 2 years. Adjusted for mortality, mean costs per patient were €31,400 for the SCS group and €23,800 for the standard group, thus 32% higher for SCS-treatment ($p=0.002$).

Discussion

Over 2 years, the costs of SCS-treatment were about €7900 (28%) higher as compared to best medical treatment alone. Initial costs in SCS-treatment were high due to device implantation. Since all other costs evolved similarly in both treatment groups, SCS-treatment remained the more expensive therapy during follow-up. Survival and amputation-free survival were similar in the two treatment groups of patients with CLI; therefore, cost-effectiveness is reduced to cost-minimisation analysis. Based on limb survival (HR=0.82), the 'number needed to treat' (NNT) to save one limb was estimated at 14, resulting in €110,000 per limb saved. Using for example a health value (utility) for below-knee amputation of 0.61,[33] this would correspond to at least €280,000 per QALY gained. Hence, from a societal perspective and with consideration of cost-effectiveness, a conservative approach as in best medical treatment is warranted.

Generally, total costs of treatment (€36,600 *vs.* 28,700 per patient over 2 years) were high. Costs of in-hospital-stay and institutional rehabilitation constituted the predominant part of the total costs of medical care in CLI. Compared with the average age- and sex-specific health care expenditure per Dutch person (€5150 annually, €10,300 over 2 years), costs are three times higher.

The TransAtlantic Inter-Society Consensus (TASC) document expressed concern about the lack of good quality data concerning cost-effectiveness of interventions in peripheral arterial occlusive disease (PAOD). Nonetheless, several groups reported data on (hospital) costs of CLI, revascularisation procedures and amputation.[24–26,34–40] On average, long-term costs following revascularisation for CLI were estimated at $23,000–28,000. Hospital costs were approximately $11,000 for successful

Table 2. Unit cost of relevant cost items in critical limb ischemia [Euro]

Direct medical cost items	Cost components	Unit cost [Euro]	
		University hospital	General hospital
In hospital			
Inpatient care (per day)	Time/attendance registration, department-based cost registration		
General ward		181	151
Intensive care unit		1150	1027
Operative procedures	Time/attendance registration, department-based cost registration		
Amputation (toe)		266	117
(Forefoot)		430	235
(Foot)		554	382
(Below-knee)		667	406
(Above-knee)		695	554
SCS-implantation	Time/attendance registration, SCS-implant, department based cost registration	7823	7760
SCS-complication treatment		715	685
Outpatient clinic (per visit)	Department based cost registrations	32	30
Routine tests on general ward (per day)	Registration in patient sample ($n=18$)	17	
Medication use on general ward (per day)	Department of vascular surgery	10	
Rehabilitation			
Consultation + follow-up (per x days)	Estimates based on reimbursement fees	$55+x\times10$	
Day-programme (per day)	Estimates based on reimbursement fees	59	
Outside hospital			
Rehabilitation centre (per day)	National Hospital Institute report	227	
Nursing home (per day)	Ministry of Health report	101	
Home for the elderly (per day)	Ministry of Health report	48	
Medical supplies, e.g.			
Crutches (per pair)	Public Health Service prices	41	
Standard wheel-chair	Public Health Service prices	559	
Below-knee prosthesis	Manufacturer's prices	1682	
Medication use (per individual patient)	Standard dose prices of recorded medicine	Spec.	
General practitioner (per visit)	Reimbursement fee	34	
Professional care, e.g.			
Day-care (per day)	Ministry of Health report	55	
Domestic social service (per hour)	Institute Medical Technology Assessment, Rotterdam	16	
Nurse (per hour)	Ministry of Health report	34	
Direct non-medical cost items			
Travel expenses (per travelled kilometre)	Kilometre price (car/public transportation/taxi)	0.20/0.09/0.60	
Time lost working	See text	–	
Out-of-pocket expenses	Social Services (for the handicapped)	150–340	
Indirect non-medical cost items			
Non-professional help (per hour)	Institute Medical Technology Assessment, Rotterdam	5.5	

revascularisation ($9000–11,000 for angioplasty, $11,000–15,000 for surgery), compared with $22,000 for failed revascularisation. Each additional procedure increased the cost by $9000. The costs for revascularisation and primary amputation were similar when the costs of a prosthesis and rehabilitative therapy were included. Primary amputation costs were reported between $17,000 and 21,000, secondary amputations lead to higher cost ($25,000–28,000).

For all important cost items, we estimated real costs rather than reimbursement fees or charges. Cost of in-hospital-stay was assessed in detail, since this was the main element of total costs of treatment. Over 80% of in-hospital days were directly related to CLI. Meticulous cost evaluation was also performed for operative procedures, but cost of amputation proved to be relatively unimportant compared to SCS-implantation. Although some differences were observed between the treatment groups as to the rehabilitation facility (rehabilitation clinic or nursing home) and the type of home care (home for the elderly or domestic professional care), combined costs for rehabilitation and home care were comparable. Due to the Dutch health care structure, costs are somewhat higher in university hospitals than in general hospitals. This does have some influence on (total) costs in university hospitals (~10% higher),

Table 3. Days spent in hospital, rehabilitation centre or nursing home in both treatment groups within 2 years after randomisation

Type of institution	Cumulative days (2 years)	
	SCS ($n=60$)	Standard ($n=60$)
In-hospital-stay		
Directly related to CLI	2523	2544
Related to CLI	480	537
Unrelated to CLI	186	39
Rehabilitation centre	623	1047
Nursing home	1607	1040

however, due to stratified randomisation this does not modify either cost comparisons between two groups or costs components (%).

A common problem when using clinical trials for any kind of cost assessment arises from the fact that the clinical protocol mandates more visits, consultations and examinations than otherwise used in clinical practice.[41] For a treatment in a research setting, there will generally be more costs, compared to daily practice. In this study, costs from protocol-driven medical care may have arisen in the outpatient costs. However, these were very limited and comprised less than 3% of the total costs.

With hindsight, all individual randomised studies on SCS for peripheral vascular disease, including the one described in this article, were underpowered. This was mainly due to the assumption that limb survival in the control group would be much lower (based on the literature data 20–40% at 1 year) and that 20–30% improvement in limb survival would be attained readily. However, the conservative (i.e. best medical) treatment groups showed much better outcomes.

A recent ‘systematic review’[18,19] included six studies, with patient numbers varying from 27 to 120 patients. The most important problem of this review was the inclusion of a ‘controlled’ (non-randomised) study by Amann.[17] In this study, patients were classified according to transcutaneous pO_2 measurements and did or did not receive SCS treatment based on this $TcpO_2$ classification and trial stimulation. Over 30% of the patients in the ‘control’ (conservative) arm underwent amputation within 2 weeks, illustrating intense selection bias. This study should be seen as a prognostic study using $TcpO_2$ measurements, rather than an adequate comparison of treatments. Remarkably, the limb survival curves were quite comparable after the initial period. In addition, amputation data input was incorrect for two studies,[22,42] the use of data from a subgroup of the smallest study[43] is artificial, and for at least three studies[42–44] concealment of treatment allocation was dubious. The value of any meta-analysis is totally dependent on lack of bias in its component studies.[45] Hence, in a meta-analysis of clinical trials, it is important to restrict inclusion to randomised trials, ideally with adequate concealment of treatment allocation, intention-to-treat analysis and objective outcome assessment. Fig. 3 shows a meta-analysis performed with amputation data input of all ($n=5$) randomised studies at 18 months, generating a risk difference for amputation of -0.07 [95% CI: -0.17 to $+0.03$] $p=0.15$ with corresponding relative risk estimate of 0.80 [95% CI: 0.60–1.06]. As regards these estimates, one should make allowance for dubious concealment of treatment allocation in three studies, which usually is associated with exaggeration of treatment effects by 40%.[46,47]

In conclusion, practical benefit from SCS as compared to best medical treatment alone in terms of

Table 4. Cumulative mean cost per patient (Euro)

Time (months)	Cost (Euro)	Hospital	Operations	Rehab	Eld. home	Homecare	Medication	Outpatient	Non-med	Total
1	SCS	2.694	7.808	17	185	171	55	123	110	11.163
3		5.425	8.041	548	545	490	253	287	260	15.849
6		7.126	8.083	3.081	1.240	816	608	420	402	21.776
12		8.586	8.131	4.740	2.547	1.549	1.092	607	599	27.851
18		10.290	8.376	5.869	3.339	1.916	1.362	772	813	32.736
24		11.799	8.376	6.759	3.803	2.316	1.483	995	1.031	36.563
1	Standard	1.695	72	54	142	306	112	98	102	2.581
3		3.982	189	1.095	308	953	439	225	215	7.405
6		6.740	278	3.839	536	1.639	1.117	351	324	14.824
12		10.990	417	6.253	814	2.559	1.806	587	470	24.167
18		11.740	417	7.323	1.226	3.197	1.958	677	555	27.093
24		12.342	417	7.484	1.341	3.695	2.010	749	627	28.665

Cost components are shown as: hospital, cost of hospital admission in-hospital stay; operations, cost of the SCS-device and implantation, amputations; rehabilitation, cost of admission to rehabilitation center or nursing home; elderly home, cost of admission to home for the elderly; homecare, cost of professional day care, general practitioner, district nurse, professional domestic help; medication, supplies, cost of medication use and medical supplies; outpatient, consultation, cost of outpatient visits, consultation for rehabilitation, prosthesis (fitting); non-medical cost, cost of non-professional help, travel expenses, out-of-pocket expenses.

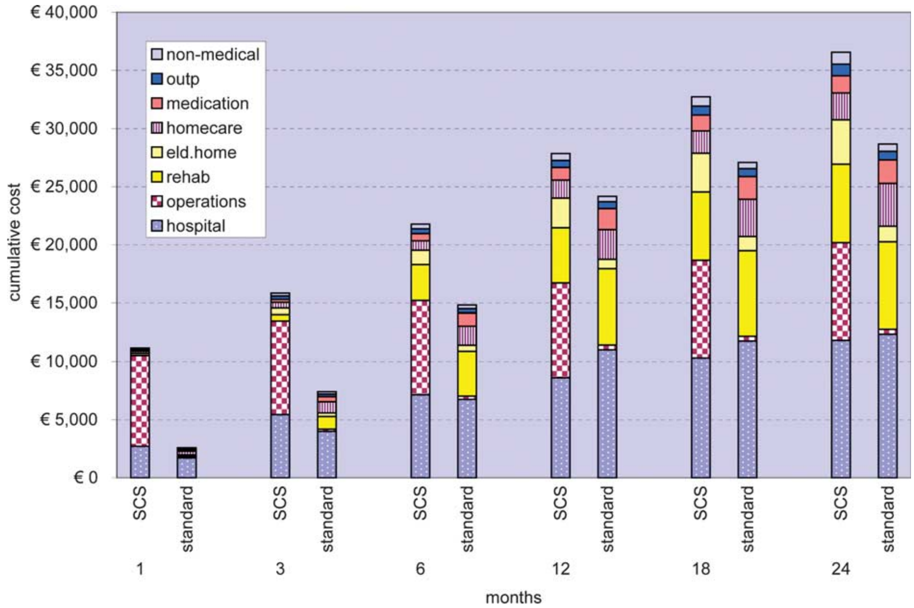

Fig. 2. Components of cumulative mean cost per patient over 2 year.

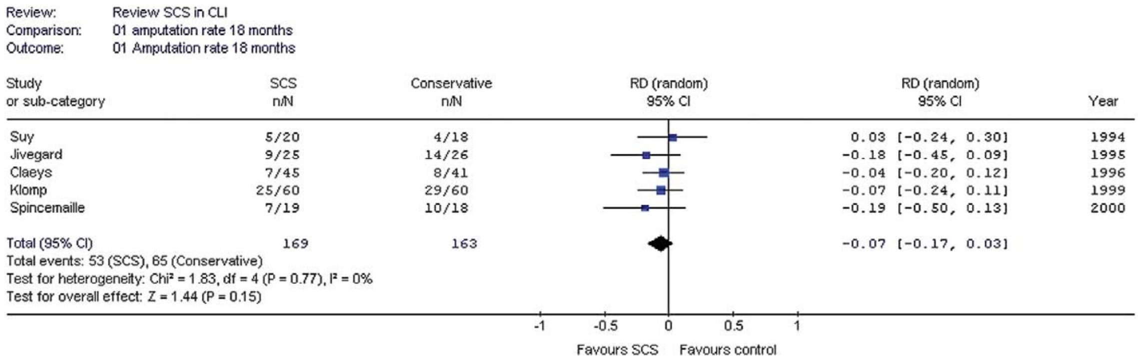

Fig. 3. Meta-analysis of randomised studies on SCS in critical limb ischaemia.

(limb) survival has not been established. If SCS is beneficial, the magnitude of the effect is small. The NNT to save one limb would be approximately 13, resulting in costs of around €100,000 per limb saved. In view of the high costs associated with limb-threatening ischaemia and its treatment, initial high costs of future therapy developments seem acceptable, particularly if substantial benefit is expected and leads to a decrease of in-hospital days and rehabilitative institutionalisation.

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